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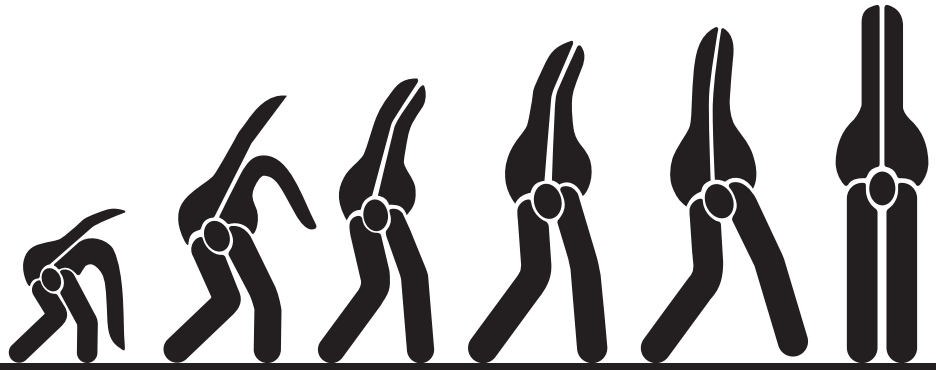

IMMUNOTHERAPY

Nice to see you — evolving MHC I–peptide presentation

One of the key processes by which transformed cells evade immunosurveillance is by restricting the intracellular peptides they present on their surface. This process is mediated by a range of MHC I molecules encoded by three different *HLA* class I genes. Many studies have addressed the response of immune cells to cancer neoantigen recognition, but less is known about how neoantigen presentation is regulated in tumour cells. Now, two studies with results published in *Cell* show that the antigen-presentation profiles of MHC I molecules influence tumour adaptation to the selective pressure of the immune system.

"The fact that few oncogenic mutations have been found to produce neoantigens in tumour samples obtained in the clinic led me to speculate that these early events might be subject to a strong immune selection during tumour initiation," explains Joan Font-Burgada, corresponding author of the first study. In collaboration with Hannah Carter, Font-Burgada developed the Patient Harmonic-mean Best Rank (PHBR) score to predict the likelihood that a patient's MHC I variants will bind to a peptide sequence containing a particular residue. Low PHBR scores indicate a high likelihood of residue presentation. This scoring system was used to determine whether individual variations in *HLA* genotypes affect the ability to present a particular mutant peptide. The *HLA-A*, *HLA-B* and *HLA-C* allele-pair genotypes were assigned for 9,176 patients with cancer using mutational data available in The Cancer Genome Atlas (TCGA).

Driver mutations were defined as those that affect known oncogenes or tumour-suppressor genes and occur in at least three tumours in TCGA. PHBR scores were higher for driver mutations than for passenger mutations. In agreement with this, a positive correlation was observed between the PHBR score of any given mutation and the frequency of that mutation in the study population. These results indicate that the presentation of passenger mutations does not subject cancer cells to high levels of selective pressure. "Immune editing of oncogenic driver mutations occurs early in tumour initiation, before the tumour can establish evasive strategies," Font Burgada points out.

In the second study, Nicholas McGranahan and Rachel Rosenthal investigated the implications of loss of heterozygosity (LOH) in the *HLA* locus. "The *HLA* locus is one of the most diverse regions in the human genome. We developed the computational tool LOHHLA to map the sequencing reads to each patient's specific *HLA* alleles instead of mapping them to the human reference genome," McGranahan remarks.

> "MHC I molecules influence tumour adaptation to the selective pressure of the immune system"

HLA LOH was found in pretreatment samples from 36 of 90 patients with lung cancer enrolled in the TRACERx study. The event was detected subclonally in 22 of 34 samples. The comparison of matched primary tumour and brain metastasis samples showed a tendency for *HLA* LOH to occur in metastases. These results suggest that *HLA* LOH occurs late in tumour evolution.

"Tumour subclones with *HLA* loss harboured an elevated nonsynonymous mutation rate. In every patient from TRACERx exhibiting *HLA* LOH, we found enrichment in neoantigens predicted to bind the lost *HLA* haplotype," reports Rosenthal. The analysis of additional samples from TRACERx revealed a higher mutational burden in tumours that exhibit *HLA* LOH compared with those without *HLA* LOH. These findings are consistent with *HLA* LOH being an immune-evasion mechanism.

Both studies have important clinical implications. "The *HLA* genotype alone provides information of which oncogenic mutations can be presented, enabling the prediction of the oncogenic mutations that a patient is most likely to acquire. For an oncogenic mutation to be frequent in human cancers, it not only needs to provide tumour fitness, but also to reside in a peptide that is poorly presented by most of human MHC I alleles," Font-Burgada summarizes. "Considering *HLA* LOH when identifying putative neoantigens that can elicit an effective T-cell response might improve the number of patients responding to immunotherapies that target specific tumour neoantigens," concludes McGranahan.

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ORIGINAL ARTICLES Marty, R. *et al.* MHC-I genotype restricts the oncogenic mutational landscape. *Cell* http://dx.doi.org/10.1016/j.cell.2017.09.050 (2017) | McGranahan, N. *et al.* Allele-specific HLA loss and immune escape in lung cancer evolution. *Cell* http://dx.doi.org/10.1016/j.cell.2017.10.001 (2017)